REMARKS

Amendments to the Specification

Applicant has furnished herewith a substitute abstract that is 149 words in length. The substitute abstract differs from the abstract of the specification as filed only in that the penultimate sentence, starting "The ellipsoidal method can also be used ...", has been deleted. Accordingly, no new matter is introduced by way of this amendment.

Applicant has also amended the title of the invention, in response to the Examiner's request.

Applicant has additionally amended the specification at page 1 to include the claim for priority, as requested by the Examiner.

In respect of the objections to the specification noted by the Examiner on the penultimate page of his Office Action, mailed September 10, 2002, Applicant has amended the specification at pages 12 and 48, wherein references to FIG. 7 are made. Applicant has also presented a substitute for page 34 of the specification as filed, attached hereto as pages 34A and 34B, to conform to the requirement of 1½ spacing of the lines.

In summary, Applicant has merely amended the specification and abstract as filed in an editorial manner, and, accordingly, no new matter is believed to be introduced by these amendments.

Amendments to the Claims

Claims 22 and 27-29 are pending in the instant application. Applicant amends claim 22 to more particularly recite and distinctly claim that which he considers to be his invention. Support for the amendment to claim 22 is found in the specification as filed at page 39, lines 1-2, and in FIG. 6 as filed.

Applicant submits that the above-made amendment is fully supported in the instant application as originally filed, and does not constitute new matter.

Rejections under 35 U.S.C. § 112 (¶ 1)

The New Matter Rejection

The Examiner has rejected claims 22 and 27-29 under 35 U.S.C. § 112 (first paragraph) for allegedly containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses the rejection.

The Examiner has pointed out three alleged deficiencies in claim 22, which Applicant addresses in turn. First, the Examiner has asserted that step (a), on pages 38-39 of the specification, is missing from claim 22. In particular, the Examiner states that claim 22 is deficient for not reciting the step of "calculation of maximal overlap of all pairs of N structures". Applicant respectfully disagrees and points out that the second step of claim 22 recites "calculating a distance matrix D wherein each element D_{ij} is a minimal metric distance ...". As stated in the specification as filed, at page 21, lines 20-25, a minimal metric distance between two molecular fields corresponds to their maximal overlap. Accordingly, it would be understood by one of ordinary skill in the art that the recitation in claim 22 of the calculation of a distance matrix in which each element is a "minimal metric distance" could be satisfied by the calculation of a "maximal overlap" for each element. It is to be understood, however, that the minimal metric distance between two molecules is not limited to a calculation of maximal overlap of their respective fields, and that the method of claim 22 is not to be so limited.

Furthermore, as one of ordinary skill in the art appreciates, a distance matrix, D, for a set of n objects, is a n by n matrix wherein each off-diagonal element, D_{ij}, is a distance between a pair of objects, specifically the object in the ith row, and the object in the jth column. Consequently, calculating such a distance matrix necessarily involves calculating each off-diagonal element, or obtaining such data from, *e.g.*, a separate prior calculation. The specification as filed, page 24, lines 12 to 14 mentions that precalculation and storage of the distances between all pairs of entries in a database is a viable technique, and indeed, one of ordinary skill in the art would recognize that such precalculation would greatly enhance efficiency and would thereby be desirable. Accordingly, the step of "calculating a distance matrix" either implicitly includes calculating distances between all pairs of objects (such as a minimal metric distance, or a maximum overlap), or may be satisfied by using values of such distances from prior calculations.

Therefore, Applicant respectfully submits that claim 22 is not missing an extra step of calculating maximal overlaps, as suggested by the Examiner, because the calculation of a distance matrix itself, as recited in claim 22, necessarily involves calculating distances

between pairs of molecules, and because the specification as filed has shown that a maximal overlap is an example of such a distance.

Second, also in respect of step (a), the Examiner has pointed out that claim 22, as filed, recited no limitation on the number of molecules, N, in the initial set. Applicant now draws the Examiner's attention to the amendment to claim 22, in which the limitation "wherein N is less than a total number of molecules in the set of molecules and is at least 2" has been introduced herein. Accordingly, Applicant respectfully submits that this amendment has rendered the Examiner's rejection moot.

Third, the Examiner has referred to the flow-chart of FIG. 6 to conclude that the choice of a field property is absent from claim 22 and should be included therein. Applicant respectfully points out that one of skill in the art would ordinarily understand that the calculations recited in claim 22 must apply to a particular property of the molecules in question. Nevertheless, for the purposes of speeding prosecution of the instant claims, Applicant has amended claim 22, herein, to include the step of choosing a property of the set of molecules. Accordingly, Applicant respectfully submits that with this amendment claim 22 avoids the new matter issues alleged by the Examiner.

The Scope of Enablement Rejection

The Examiner has also rejected claims 22 and 27-29 under 35 U.S.C. § 112 (first paragraph) because the specification allegedly "does not reasonably provide enablement for any construction utilizing a generic distance geometry technique" or "any generic diagonalizing of G to obtain a set of positions in N-1 dimensional space." Instead, the Examiner asserts that the specification is only enabling for the aforementioned constructing and diagonalizing steps as set forth in the Blaney *et al.* reference (hereinafter "Blaney") recited on page 39 of the specification. Applicant respectfully traverses the rejection.

The Examiner has cited *In re* Wands (CAFC, 1988) for providing 8 factors (the "Wands factors") that are to be considered when deciding whether undue experimentation would be required to practice the claimed invention. However, rather than identify specific Wands factors, the Examiner claims to have provided discussion for "a sufficient amount for a *prima facie* case." In essence, the central thesis of the Examiner's rejection is that one of skill in the art would be required to indulge in "undue experimentation" (Wands factor no. 1)

because the calculations in question are of "significant complexity" and that any method not disclosed in Blaney would be "unpredictable" (Wands factor no. 7).

While the Wands factors are instructive, the Federal Circuit has continued to address the issue of enablement in broadly applicable terms. In particular, "[t]he purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art." *Scripps Clinic & Res. Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991). Thus, it remains true that the touchstone of enablement is the amount of information the artisan of ordinary skill would need in order to carry out the claimed invention, and whether that information can be found from the patent specification in combination with his/her general knowledge.

Accordingly, Applicant respectfully points out that the calculations in question are within the capability of one of ordinary skill in the art, and that the reference to Blaney is not for the purpose of indicating the applicability of a number of unspecified methods, but to provide one of ordinary skill in the art with a reference that describes the routine manner of operation of the distance geometry technique.

The Content of Blaney

Applicant first respectfully points out that Blaney presents a general description of core features of the distance geometry technique (*e.g.*, Blaney, p.304), and further directs an interested reader to a large number of literature citations wherein uses of the distance geometry technique may be found. Applicant is making a copy of Blaney available to the Examiner in an Information Disclosure Statement accompanying this response. Although distance geometry can be applied in a number of different circumstances, there are several salient aspects of distance geometry that are common to all implementations. Such salient aspects are found in Blaney. Indeed, Blaney was recited by Applicant in the specification as filed as an indication of general level of knowledge in the art from where a typical implementation of the specific steps recited in claim 22 could be found (see the language on p.39, lines 9-11 of the specification as filed: "... as described in *any* description of distance geometry, *e.g.*, Blaney and Dixon ..." (emphasis added)). Thus, construing Applicant's

claims to be limited to the disclosures of Blaney does no more than construe them to be limited to distance geometry itself, as further described hereinbelow.

Furthermore, as can be seen, Blaney is a review article and describes a number of applications of distance geometry in the art of computational chemistry. Thus, Blaney demonstrates that distance geometry is a method that has been frequently implemented and used by computational chemists.

The Alleged Unpredictability of Unspecified Distance Geometry Methods

In general, with respect to the various steps set forth in claim 22, certain steps are ordinarily considered to be straightforward in nature, and require no special skill or considerations for their implementation beyond what one of ordinary skill in the art possesses. Steps (c) and (e), on page 39 of the specification as filed, are of this nature and, for this reason, Applicant considered it sufficient to direct a reader to a reference such as Blaney for recitation of the applicable formulae.

With respect to the Examiner's specific allegation that the step of "constructing a metric matrix G from D" (step (c)) is an "undirected and random process if not defined by a conversion algorithm and thus unpredictable", Applicant directs the Examiner to the teaching of Blaney. Distance geometry defines a single approach to deriving the matrix, G, from D: first the distance d_{io} between each point i and the 'center of mass' of all of the points is calculated:

$$d_{io}^2 = \frac{1}{N}\sum_{i=1}^{N} d_{ij}^2 - \frac{1}{N^2}\sum_{j=2}^{N}\sum_{k=1}^{j-1} d_{jk}^2$$

– *i.e.*, according to formula [4], on page 306 of Blaney (which refers to atoms, rather than points, but is analogous to Applicant's situation). Then, as further discussed on page 306 of Blaney, G is calculated from the well-known law of cosines, using elements, d_{ij}, of D and the distances d_{io}. Because these formulae are used in all distance geometry applications, there is therefore no unpredictability arising from a possible choice of alternatives.

Thus, not only would one of ordinary skill in the art appreciate that a well-defined formula exists to achieve the transformation from D to G set forth in Applicant's claim, but one of ordinary skill in the art would also appreciate that there would be little unpredictability in application of such a formula.

With respect to the Examiner's assertion that the "diagonalizing step to obtain a set of positions in N–1 dimensional space" is "random and unpredictable", where not described by Blaney, Applicant also respectfully disagrees. Again, there is a single reliable way to obtain the set of positions using principles of distance geometry. As discussed in Blaney, although in practice G is obtained from D via a standard formula of distance geometry, G is also, by definition, a product of a matrix of coordinates, X, and its transpose:

$$G = XX^T$$

(as given by Blaney at p.304, equation [1]). These two ways of expressing G are used, in distance geometry, to derive the set of positions. It is an elementary mathematical principle that G, a symmetric matrix, can be placed in diagonal form:

$$G = VL^2V^T$$

i.e., as in equation [2] on p.305 of Blaney, wherein V is a matrix whose columns are eigenvectors of G, and the diagonal elements of L^2 are the eigenvalues of G. This being so, the matrix of coordinates, X, is then expressible in terms of a simple product of the matrix of eigenvalues and the matrix of eigenvectors of G:

$$X = VL$$

(as given in equation [3], on p.305 of Blaney).

Accordingly, one of ordinary skill in the art appreciates that, having obtained G, the step of obtaining the matrix of coordinates, X, is not "random and unpredictable" but is, in fact, dependent only upon the very reliable technique of matrix diagonalization (a technique that the Examiner has acknowledged to be "well-known", Office Action, page 5).

Finally, with regard to the N-1 dimensionality of the problem described by Applicant, the "significant complexity" alleged by the Examiner is vitiated by the observation that the methods of matrix diagonalization and multiplication, as discussed hereinabove, are straightforward to apply in any imaginable dimensionality, subject to appropriate computational resources.

In summary, Applicant respectfully submits that a computational chemist of ordinary skill would understand, from reading a reference such as Blaney, how to implement the key features of the distance geometry method that are pertinent to practicing the claimed invention because Applicant has identified just which steps are to be used and becuase the nature of those steps is widely known.

The Lack of Enablement Rejection

The Examiner has also rejected Claims 22, and 27-29 under 35 U.S.C. § 112 (first paragraph), for allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make or use the invention. The Examiner has asserted that "the incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper" and requested that Applicants amend the disclosure to include the material incorporated by reference. The specific material that the Examiner seeks to have added to the specification is details of the prior art distance geometry methods.

Applicant asserts that, according to the remarks concerning scope of enablement, presented hereinabove, the specification as filed is enabling to one of ordinary skill in the art because the distance geometry methods specified by the Examiner are within the knowledge and skill of one of ordinary skill in the art. Therefore, Applicants respectfully submit that it is not necessary to incorporate into the specification the distance geometry method stated by the Examiner.

The level of skill in Computational Chemistry in the use of Distance Geometry

The test of enablement is that the disclosure should be adequate to one skilled in the art. "Enablement is determined from the viewpoint of persons of skill in the field of the invention at the time the patent application was filed." *Ajinomoto Co., Inc., v. Archer-Daniels-Midland Co.*, 228 F.3d 1338 (Fed. Cir. 2000). As discussed hereinabove, Blaney illustrates that the distance geometry method was known to, and widely practiced by, those of ordinary skill in the art prior to Applicant's filing date.

To this end, Applicant points out that the standard by which one of ordinary skill in the art should be measured is that applicable to *computational* inventions. "When the challenged subject matter is a computer program that implements a claimed device or method, enablement is determined from the viewpoint of a skilled programmer using the knowledge and skill with which such a person is charged." *Northern Telecom, Inc., v. Datapoint Corp.*, 908 F.2d 931 (Fed. Cir. 1990). In *Northern Telecom*, the Federal Circuit further held: "[t]he amount of disclosure that will enable practice of an invention that utilizes a computer program may vary according to the nature of the invention, the role of the

program in carrying it out, and the complexity of the contemplated programming, all from the viewpoint of the skilled programmer."

Furthermore, Applicant respectfully points out that, "[e]nablement is determined from the viewpoint of persons of skill in the field of the invention at the time the patent application was filed." *Ajinomoto Co., Inc., v. Archer-Daniel-Midland Co.*, 228 F.3d 1338 (Fed. Cir. 2001). In order to establish that a specification is enabling, a patent applicant may offer evidence, such as patents and publications, to demonstrate the knowledge which is possessed, as of the filing date, by those skilled in the art. *In re Eynde, Pollet & de Cat*, 178 U.S.P.Q. 470, 474 (C.C.P.A. 1973). In this case, Blaney suffices for this purpose because it represents an overview of the state of the art prior to Applicant's filing date. Blaney provides evidence that distance geometry is not only widespread in the art of computational chemistry, but susceptible to a number of different applications (in, *e.g.*, NMR, conformational analysis, or drug-receptor docking, see Blaney, p.299). In this regard, Applicant submits that the existence of such a plethora of applications of distance geometry (as discussed in Blaney) demonstrates that an understanding of distance geometry would be accessible to a computational chemist of ordinary skill in the art of computer program development at the time the application was filed. Thus as a matter of law, Applicant's specification may presume such knowledge, and is therefore enabling with respect to the distance geometry technique.

Furthermore, in requesting the Applicant to amend the specification to include specific details of a distance geometry method, the Examiner is exceeding the general requirements of enablement according to the first paragraph of 35 U.S.C. § 112, since the patent should be addressed to one skilled in the art. As the case law of the Federal Circuit has shown,"[a] patent need not teach, and preferably omits, what is well known in the art." *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987). Thus, "[a] patent document is not a scientific treatise, but a document that presumes a readership skilled in the field of the invention." *Ajinomoto*, at 1347.

Accordingly, Applicant respectfully submits that he has more than satisfied the statutory requirements of 35 U.S.C. § 112 (¶ 1) by offering in the specification as filed a literature citation to applicable methods of distance geometry, especially considering that the theory behind the methods is both well known and has been accessible to one skilled in the art for long before Applicant's filing date. Such material would unduly weigh down

Applicants' patent were it to be incorporated by amendment. In particular, the Federal Circuit has recently held:

> The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. *** To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. ('The specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel.')

S3 Inc. v. nVIDIA Corp., 259 F.3d 1364 (Fed. Cir. 2001) (citations omitted).

Furthermore, the Examiner is respectfully reminded that the "reason for the incorporation by reference practice ... is to provide the public with a patent disclosure which minimizes the public's burden to search for and obtain copies of documents incorporated by reference which *may not be readily available*." MPEP § 608.01(p); [emphasis supplied by Applicants.] To this end, Applicant wishes to make clear that the cases cited by the Examiner in support of his position (*In re Hawkins*, 486 F.2d 569 (C.C.P.A., 1973); *In re Hawkins*, 486 F.2d 579 (C.C.P.A., 1973); *In re Hawkins*, 486 F.2d 577 (C.C.P.A., 1973)) are distinguishable from the situation for the instant application. In each of the cases cited by the Examiner, the material that Applicant sought to incorporate by reference was only to be found in copending British patent applications that were *not available to the public*. Accordingly, in such circumstances, it was appropriate to require the specification to be amended because the referenced material was not in the public domain. By contrast, in the instant application, Applicant is directing an artisan of ordinary skill to a work of reference that is publicly available for the purposes of illustration.

In summary, it would be well within the capabilities of one of ordinary skill in the art to use pertinent information from published or commercially available references, such as Blaney and references disclosed therein, that described the distance geometry technique, when practicing Applicant's invention. Therefore, Applicant respectfully submits that the specification is fully enabling with respect to the use of distance geometry techniques for practicing Applicant's claimed invention.

Rejections under 35 U.S.C. § 112 (¶ 2)

The Alleged Lack of Commensurate Scope

The Examiner has rejected claims 22 and 27-29 under 35 U.S.C. § 112 (second paragraph) as being allegedly indefinite for failing to particularly point out and distinctly

claim Applicant's invention. In particular, the Examiner has asserted that the wording of claim 22 is not commensurate in scope with the language on pages 38 and 39 of the specification as filed, and has requested clarification via clearer claim wording.

Applicant respectfully draws the Examiner's attention to the amendments to claim 22, presented herein, and Applicant's remarks hereinabove addressing the Examiner's new matter rejection under 35 U.S.C. § 112 (first paragraph). Specifically, language present in the specification at pages 38 and 39, and in FIG. 6, has been incorporated by amendment into claim 22, and Applicant has argued hereinabove that claim 22 adequately recites calculation of a distance matrix. Accordingly, Applicant respectfully submits that upon consideration of the amendments and remarks presented herein, the Examiner should be in a position to remove his rejection of claims 22 and 27-29 under 35 U.S.C. § 112 (second paragraph).

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 22 and 27-29 under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. According to the Examiner, "a process consisting solely of mathematical operations ... does not manipulate appropriate subject matter and thus cannot constitute a statutory process" (citing to *In re Warmerdam*, 33 F.3d 1354 (Fed. Cir. 1994)). Applicant respectfully traverses the rejection because the Examiner has not stated the current standard under applicable law.

Applicant respectfully submits tthat the standard of patentability for computer-based inventions is that set forth in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.* 149 F.3d 1368 (Fed. Cir. 1998). *State Street Bank* concerned a patent for a data processing system used in the financial services industry. In *State Street Bank*, the Federal Circuit set forth its standard for the patentability of mathematical algorithms:

> [W]e hold that the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces a 'useful, concrete and tangible result'.

Accordingly, it is not the form of the manipulations embodied in the claims, but the outcome of their application, upon which patentability is judged. The court in *State Street Bank* went on to conclude that "[t]he question of whether a claim encompasses statutory subject matter should not focus on which of the four categories of subject matter a claim is directed to ... but

rather on the essential characteristics of the subject matter, in particular, its practical utility." Thus, the current standard of patentability for computer-based inventions is whether or not they are useful.

As set forth in Applicant's specification as filed, Applicant's recited claim is useful because it permits concise representation of molecular properties, and facilitates the searching of large databases of molecules. (specification as filed, page 5, lines 1-6.) The warehousing of molecular structural data in computer databases has long been a reality of daily life in organizations such as pharmaceutical companies. (Specification as filed, page 2, lines 7-8.) Furthermore, the efficient searching of such databases for molecules of particular characteristics is an important goal. (Specification, page 2, lines 13-14.) Applicant's claimed invention is useful for just such a purpose and Applicant respectfully submits that such a purpose is a sufficient practical utility to satisfy the requirements of 35 U.S.C. § 101. Accordingly, Applicant respectfully requests that the Examiner remove his rejection of record.

Conclusion

With this Amendment, Applicant has amended claim 22. Applicants respectfully submit that Claims 22 and 25-27 meet all of the requirements for patentability and are in condition for allowance. An early allowance is earnestly requested.

The Commissioner is hereby authorized to charge any additional fees associated with this paper communication or credit any overpayment to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date March 10, 2003

Francis E. Morris 24,615

Francis E. Morris (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures

APPENDIX A:
CHANGES TO SPECIFICATION UPON ENTRY OF AMENDMENT
Mailed, March 10, 2003

U.S. PATENT APPLICATION SERIAL NO. 09/644,937
(ATTORNEY DOCKET NO. 9476-003-999)

The following mark-up scheme is adopted:
Deleted material: Strike-through.
Inserted material: Bold Underline

On Page 1, line 1, *please amend the Title as follows*:

METHOD ~~AND APPARATUS~~ FOR ~~EVALUATING MOLECULAR SIMILARITY~~ **DETERMINING A SHAPE SPACE FOR A SET OF MOLECULES USING MINIMAL METRIC DISTANCES**

On page 12, amend the paragraph beginning at line 27, as follows:

~~Fig. 7 is a~~ **Figs. 7A and 7B show** flow ~~chart~~ **charts** illustrating a third aspect of the invention.

On page 48, amend the paragraph beginning at line 17, as follows:

As illustrated in the flow chart of ~~Fig. 7~~ **Figs. 7A and 7B**, the closest structure is found by the following steps:

On Page 74, amend the Abstract beginning at line 3 in the following way.

I describe several techniques for characterizing molecules based on the shapes of their fields. The minimal distance between two molecular fields is used as a shape-based metric, independent of the underlying chemical structure, and a high-dimensional shape space description of the molecules is generated. I then show how these attributes can be used in creating, characterizing, and searching databases of molecules based on field similarity. In particular, they allow searches of a database in sublinear time. Next, I extend the utility of this approach by describing a way to automatically break molecules into a series of fragments by using an ellipsoidal Gaussian decomposition. Not only can these fragments then be analyzed by the shape metric technique described above, but the parameters of the

decomposition themselves can also be used to further organize and search databases. ~~The ellipsoidal method can also be used to describe binding or active sites on macromolecules, providing a template for searching for complementary molecules in a database such as I describe.~~ The most immediate application of these techniques is to pharmaceutical drug discovery and design.

APPENDIX B:
CHANGES TO CLAIMS UPON ENTRY OF THE AMENDMENT
Mailed, March 10, 2003

U.S. PATENT APPLICATION SERIAL NO. 09/644,937
(ATTORNEY DOCKET NO. 9476-003-999)

The following mark-up scheme is adopted:
Deleted material: Strike-through.
Inserted material: Bold Underline

22. (Amended) A method of determining a shape space of a set of molecules, comprising:

choosing an initial set of N molecules **wherein N is less than a total number of molecules in the set of molecules and N is at least 2, and a property of the set of molecules**;

calculating a distance matrix D wherein each element D_{ij} is a minimal metric distance between **said property of** a molecule i and **said property of** a molecule j and wherein said molecule i and said molecule j are in said initial set of molecules;

constructing a metric matrix G from D according to a distance geometry technique;

diagonalizing G, thereby obtaining eigenvalues of G, and obtaining a set of positions in N-1-dimensional space that reproduce the distances in said matrix D to within a tolerance T, wherein each position of said set of positions has N-1 coordinates associated with it;

determining which of the N-1 coordinates that represent positions in shape space of each of the N molecules can be eliminated for every molecule such that a remaining number, M, of the N-1 coordinates still enables said distance matrix to be reproduced to within said tolerance, T; and

defining the shape space to be an M dimensional subspace occupied by the N molecules.